encoded by a DNA sequence selected from the group consisting of the DNA sequences set forth in Fig. 16 A. Fig. 16 C, Fig. 16 E and Fig, 16G.

60. The fully human IgG2 antibody according to claim 59, further comprising a kappa light chain with the amino acid sequence encoded by a DNA sequence selected from the group consisting of the DNA sequences set forth in Fig. 16B, Fig. 16D, Fig. 16F and Fig. 16H.

61. The method according to claim 56, wherein the desired antigen is PTHrp.

62. The yH1C YAC having ATCC accession number 74367.

REMARKS

Applicants have amended the specification to correct inadvertent typographical errors. Applicants have cancelled claim 45, without prejudice, and have added claims 46-62. Applicants reserve the right to prosecute the subject matter of the canceled claim in future applications claiming priority from the present application under 35 U.S.C. § 120.

Claim 46 is directed to a transgenic mouse and progeny, wherein all of the somatic and germ cells comprise a fragment of human chromosome 14 from the five most proximal V_H gene segments, continuing through the D segment genes, the J segment genes and the constant region genes through Cδ of the human immunoglobulin heavy chain locus, wherein said fragment does not contain a Cγ gene, and wherein said fragment is operatively linked to a human Cγ2 region gene, said transgenic mouse producing fully human IgG2 heavy chains specific for a desired antigen when immunized with said desired antigen. Support for this claim

may be found in the specification at page 6, lines 9-18.

Claim 47 adds that the somatic and germ cells of said transgenic mouse further comprise a fragment of human chromosome 2 comprising Vκ, Jκ and Cκ gene segments of an immunoglobulin kappa light chain locus, said transgenic mouse producing fully human IgG2 antibodies specific for a desired antigen when immunized with said desired antigen. Support for this claim may be found in the specification at page 6, lines 9-21.

Claims 48 and 49 recite that the human heavy chain DNA is the human DNA contained in the yH1C YAC having ATCC accession no. 74367. Claim 62 is directed to the yH1C YAC. Support for these claims may be found in the specification at page 6, lines 13-18; page 43, lines 2-8 and Figure 1.

Claims 50 and 51 recite that the human kappa light chain DNA extends from the three most proximal Vκ gene segments, continuing through the Jκ and Cκ gene segments, through the human kappa deleting element. Support for these claims may be found in the specification at page 6, lines 11-13, referring to Green et al., *Nature Genetics*, 7, pp. 13-21 (1994) ("Green"), which is incorporated by reference (page 42, lines 25-29). See Green, p. 13, right column, and Fig. 1c.

Claims 52 and 55 are directed to a transgenic mouse and progeny comprising inactivated endogenous immunoglobulin heavy and light chain loci. Support for this claim may be found in the specification at page 3, lines 4-6; page 5, line 31 to page 6, line 2.

Claims 53 and 54 are directed to a transgenic mouse and progeny, wherein all of the somatic and germ cells comprise a portion of an unrearranged human immunoglobulin heavy chain locus and an unrearranged portion of a human immunoglobulin kappa light chain locus, wherein said transgenic animal when immunized with a desired antigen

produces high affinity fully human IgG antibodies specific for said desired antigen, said high affinity antibodies being characterized by dissociation constants (K_d) of 2×10^{-9} or less or 10^{-10} or less, respectively. Support for this claim may be found throughout the specification, for example at page 6, lines 2-35 and page 35, line 35 to page 36, line 38 and Table 4.

Claims 57, 58 and 61 recite the method of the invention, wherein the desired antigen is selected from a group of recited antigens, or is human IL-8 or PTHrp. Support for these claims may be found in the specification at page 16, line 7 to page 18, line 5; Example 7 (pages 30-31); Examples 8-9 (pages 31-42) and claims 20, 26, 27, 30 and 39 as originally filed.

Claims 59 and 60 are directed to a fully human antibody comprising heavy and light chains encoded by a DNA sequence provided in Fig. 16.

None of the amendments adds new matter. Applicants request entry of the amendments and reconsideration and allowance of the pending claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 45 stands rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement in the specification. Specifically, the Examiner asserts that "the instant specification fails to disclose a transgene capable of undergoing isotype switching." The Examiner further asserts that the specification is "merely prophetic of all aspects of the transgene", that the "instant specification" is not enabling for the human IgH locus containing the V, D, J, mu, delta and gamma sequences cloned into a YAC capable of undergoing isotype switching, nor for a transgenic animal containing the IgH locus YAC.

Finally, the Examiner asserts that:

"the specification of the instant application regarding the actual production of transgenic mice containing human immunoglobulin genes produced by fusion of spheroplasts containing YACs with ES cells is speculative and does not present any working examples showing actual cloning of human immunoglobulins (monoclonals) and that if such mice were actually obtained, that human antibodies would be expressed from the IgH locus."

Applicants' cancellation of claim 45, without prejudice, obviates this rejection.

Claims 46-62 are fully enabled by the application as filed. The application, as filed, provides working examples demonstrating the production of fully human IgG antibodies specific for a desired antigen in the serum of transgenic mice. See Example 2 (human TNFα); Example 7 (PTHrp); Example 8 (human IL-8).

The specification, as filed, provides a working example of the production of fully human IgG monoclonal antibodies from the spleen cells of transgenic mice of the invention immunized with human IL-8. Those monoclonal antibodies have high affinities as measured by, *inter alia*, the dissociation constant (K_d). It will be understood that an antibody with high affinity will have a dissociation constant with a low value. As the affinity increases, the value of the dissociation constant decreases. Table 4 provides data demonstrating that the fully human anti-IL8 monoclonal antibodies of the invention have dissociation constants of 2×10^{-9} or less.

In view of the teachings in the application, as filed, claims 46-62, are fully enabled.

Rejection Under 35 U.S.C. § 102(e)

Claim 45 stands rejected under 35 U.S.C. § 102(e) as "anticipated" by United States patent 5,545,806 (Lonberg et al.) ("Lonberg"). The Examiner asserts that Lonberg "discloses the invention exactly as claimed."

Applicants' cancellation of claim 45, without prejudice, obviates this rejection. Lonberg does not disclose the mice, methods, antibodies or YACs of the invention.

Claims 46-58 and 61 recite, in part, a transgenic mouse and progeny, wherein all of the somatic and germ cells comprise a fragment of human chromosome 14 from the five most proximal V_H gene segments, continuing through the D segment genes, the J segment genes and the constant region genes through Cδ of the human immunoglobulin heavy chain locus, wherein said fragment does not contain a Cγ gene, and wherein said fragment is operatively linked to a human Cγ2 region gene, or methods comprising said transgenic mouse. Lonberg does not disclose such a mouse.

Lonberg is directed to the production of a transgenic mouse utilizing engineered "miniloci". Lonberg refers to a "discontinuous genomic" heavy chain transgene constructed from an 85 kb SpeI fragment of a human heavy chain locus (Example 16). That fragment contains only one VH gene and only part of the Cδ gene. The Example also refers to a putative 570 kb NotI fragment from the heavy chain variable region. Lonberg never exemplifies a transgenic mouse containing either of those fragments. Even if such a mouse were exemplified, it is not a mouse of the present invention.

Lonberg also refers to a 670-830 kb NotI fragment of the human heavy chain (Examples 1 and 17; Figure 4). That fragment spans a portion of the V region, the D and J regions and encompasses all of the constant region genes, including the Cγ1-4 genes. In contrast, the fragment of the human heavy chain locus referred to in claims 46-58 and 61 explicitly excludes any Cγ genes.

The reference in Lonberg to a YAC containing the NotI fragment does not anticipate applicants' invention for

another reason. At the time Lonberg was filed, the NotI fragment had not been successfully isolated intact. In fact, the Examiner noted in connection with the rejection under § 112, first paragraph, that a method utilizing YAC technology with the NotI fragment was not enabled absent evidence of the actual cloning and insertion of the YAC into a mouse. In making this rejection, the Examiner relied on a Declaration of Diane Cox, of record in the application from which Lonberg issued. According to the Examiner:

> "the Cox declaration states that there were no reports of the cloning in YAC vectors of the region spanning the human delta and gamma-3 genes. This region is not readily or predictably cloned and the problem, as explained by the declarant, is possibly due to instability of that region of the human genome in certain cloning vectors, such as YACs."

The method using YAC technology and the NotI fragment referred to prophetically in Lonberg, thus, is not enabled. Accordingly, it cannot destroy the novelty of applicants' invention.

Finally, Lonberg does not disclose human IgG antibodies having an amino acid sequence encoded by the DNA sequences set forth in Figure 16. Nor does Lonberg disclose the yH1C YAC having ATCC accession No. 74367.

Claims 46-62, thus, are novel over Lonberg.

In view of the above, applicants request reconsideration and allowance of the pending claims.

Respectfully submitted,

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